Pancreatic Cancer - Synthesis of Anticancer Therapies

6 Dec. 2021

Pancreas
- Glandular organ in the abdomen
- Makes pancreatic juices (contain digestive enzymes)
- Produces hormones (e.g. insulin)


Pancreatic Cancer
- 7th most deadly cancer, 5% survival rate
- Affects 496,000 people globally, causing 466,000 deaths in 2020
- Projected to surpass breast cancer as 3rd leading cause of cancer death by 2025

Most Common Pancreatic Cancer Chemotherapies
- FOLFIRINOX
  - 5-fluorouracil, folinic acid, irinotecan, and oxaliplatin
- gemcitabine
- nanoparticle albumin-bound paclitaxel (nab-paclitaxel)

Treatments
- Surgical resection → only chance for cure
  - Subsequent chemotherapy improves long-term outcomes
- Almost 85% of patients are not eligible for surgical resection
  - Few who are eligible risk a 66–92% chance of recurrence within 2 years of the surgery
- Chemotherapy remains main form of treatment for patients with advanced pancreatic cancer

Why?
- Lack of early diagnostic tools → late diagnosis
  - Symptoms early on are vague or not present

**Chemotherapy mechanism of action**

**Mitotic spindle inhibitors**
- prevent cell division from occurring correctly

**Topoisomerase inhibitors**
- induce cell death by compromising topoisomerase activity (essential for DNA replication)

**Other**
- enzyme inhibitors
  - compounds that:
    - generate free radicals
    - inhibit the degradation of proteins that lead to cell death

**Alkylating agents**
- alkylate DNA and create crosslinks within/between strands
- results in mispairing of bases and prevention of DNA strand separation during synthesis

**Antimetabolites**
- compounds that:
  - affect key biosynthetic pathways
  - affect the synthesis of DNA and RNA from occurring correctly

---

**Gap in knowledge**
Only modest progress in pancreatic cancer treatments over last decade

Greater than 90% of patient deaths (for all cancer, not specific to pancreatic) are due to the resistance of cancer cells to the chemotherapy

**Potential Solution**
- Develop new screening strategies for high-risk patients to detect pancreatic tumours at earlier stages
- Identify new enzymes in cancer cells to target, and develop inhibitors for these targets that can be used as novel therapies and alternative treatment strategies


5-fluorouracil
- Antimetabolite chemotherapy
- used to treat > 2 million patients
- 4200+ related publications and patent applications
- Metabolism of 5-fluorouracil generates fluorodeoxyuridylate which inhibits thymidylate synthase, causing cell death

First synthesis: Heidelberger (1957)

Industrial synthesis: Baasner and Klauke (1989)

**Folinic acid**
- Often administered in addition to 5-fluorouracil
- Inhibitor to many folate dependent enzymes
- Derivative of folic acid, a necessary vitamin to mammals

**Synthesis: Roth et al. (American Cyanamid Company, 1952)**

![Chemical structure of folic acid and synthesis](image)

**Oxaliplatin**
- Used to treat a variety of cancers
- Causes inter- and intra-strand crosslinks in DNA, thereby inhibiting DNA synthesis

**Synthesis: Khokhar (1994)**

![Chemical structure of oxaliplatin and synthesis](image)

**Nab-paclitaxel (nanoparticle albumin-bound taxol):**
- Prevents division by promoting microtubule assembly
- Bound to human serum albumin using high-pressure homogenization of taxol in the presence of albumin
- Taxol is hydrophobic – requires use of Cremophor EL (CrEL) to deliver drug
  - CrEL can cause acute hypersensitivity reactions and neurological toxicity
- Nab-paclitaxel developed to improve the solubility of taxol (doesn’t require use of CrEL)
- Tumor cells actively take up albumin via active transport due to increased nutrient need
  - increases concentration of nab-paclitaxel in tumor cells
  - improves the toxicity of the drug
- Nab-paclitaxel can be administered in 30 mins vs 3 h for CrEL-bound taxol

**Cancer Chemother. Pharmacol. 2005, 55, 301–305.**

**Expert Opin. Pharmacother. 2010, 11, 1413-1432.**
**Future Oncol. 2005, 1, 755-762.**
Pancreatic Cancer - Synthesis of Anticancer Therapies

Irinotecan
- Synthetic analog to naturally occurring alkaloid camptothecin
- Inhibits DNA topoisomerase I
- Carbamate hydrolyzed by carboxylesterase into highly active metabolite, SN-38

Retrosynthetic analysis: Henegar (Pharmacia & Upjohn, 1997)

Synthesis


Camptothecin
- Isolated in 1958 from *Camptotheca acuminata* (a tree native to China and Tibet)
- Used in traditional Chinese medicine
- First total synthesis of naturally occurring S enantiomer by E. J. Corey in 1975
- Less water-soluble than irinotecan

Retrosynthetic analysis: Corey (1975)

Synthesis

Pancreatic Cancer - Synthesis of Anticancer Therapies

Alina J. Cook

6 Dec. 2021

Gemcitabine
- Prodrug
- Active form → di- and triphosphate
- Inhibits DNA synthesis thereby causing cell death
- Lilly Research Laboratories branded drug as HCl salt (Gemzar)
- With patent, $1 billion/year drug
- Used to treat a variety of cancers including pancreatic, ovarian and breast cancer
- Patent has expired and has led to the development of alternative approaches

Retrosynthetic analysis: Hertel (Lilly Research Laboratories, 1988)

Carbohydrate Research. 2015, 406, 71-75.
Pancreatic Cancer - Synthesis of Anticancer Therapies

Synthesis

D-mannitol

\[ \begin{array}{c}
\text{HO-CH(OH)-CH(OH)-CH(OH)-CH(OH)-OH} \\
\text{ZnCl} \quad \text{acetone} \\
\text{rt, 3 h}
\end{array} \]

\[ \begin{array}{c}
\text{Me} \\
\text{Me}
\end{array} \]

\[ \begin{array}{c}
\text{OH-CH(OH)-CH(OH)-CH(OH)-CH(OH)-OH} \\
\text{Pb(OAc)\textsubscript{4}} \\
\text{Et\textsubscript{2}O/THF} \\
\text{reflux, 30 min}
\end{array} \]

\[ \begin{array}{c}
\text{Me} \\
\text{Me}
\end{array} \]

\[ \begin{array}{c}
\text{OH} \\
\text{Et\textsubscript{2}O/THF} \\
\text{reflux, 30 min}
\end{array} \]

major diastereomer

Dowex 50

rt, 4 days

J. Biol. Chem. 1939, 128, 463-473.

Irofulven

- Novel, experimental chemotherapy
- Undergoing phase I and II clinical trials to treat a variety of cancers
- Alkylating agent
- Inhibits DNA synthesis via cyclopropyl ring opening

Gemcitabine

Irofulven

Retrosynthetic analysis: Movassaghi (2006)
Pancreatic Cancer - Synthesis of Anticancer Therapies

Synthesis

Alina J. Cook 6 Dec. 2021

Novel Therapies

- **Vatalanib**
  - Used in phase II trial with gemcitabine

- **Sorafenib**
  - Used in phase II trial with and without gemcitabine

- **Axitinib**
  - Used in phase II trial and 2 x as potent as taxol

- **Ixabepilone**
  - Used in phase I/II trial with gemcitabine

- **AZM475271**

Summary

- Most common pancreatic cancer chemotherapies are FOLFIRINOX (5-fluorouracil, folinic acid, irinotecan, and oxaliplatin), gemcitabine, and nab-paclitaxel
- Novel chemotherapies include irofulven and others

Future directions

- Develop new screening strategies for high-risk patients to detect pancreatic tumours at earlier stages
- Further exploration of novel compounds as new chemotherapies

Useful reviews

- Pancreatic cancer:
- Treatments:
- 5-fluorouracil:
- Camptothein and derivatives:
- Novel treatments: